Metabolism and lipid mediators as regulators of innate immune cell function: implications for inflammation and immune responses

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I

General Introduction

Macrophages and Dendritic Cells as Key Regulators of Immune Responses

The immune system is the main line of defence against the millions of potential pathogens (1–3) and other challenges, such as possible cancerous cells and allergens, humans are exposed to on a daily basis (4–7). This system is a complex and intricate network of many different molecules, cells, tissues, and organs, all working in tandem, in a tightly regulated manner, albeit with different functions and mechanisms of action. The immune system can be divided into two main parts – the innate immune system and the adaptive immune system. The innate immune system acts in a fast and broad manner, with general specificity, being activated by generic conserved molecular motifs, such as PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns). Conversely, the adaptive immune system, although slower to act, is highly precise and efficient, recognizing a specific antigen, thus being able to zone-in on an individual type of pathogen or molecule (8).

However, without the initial input of the innate immune system, the adaptive immune system cannot be activated (9,10). This makes the innate immune system a key player in the overall immune response. Therefore, unravelling the mechanisms of action which govern innate immune cell function poses as an imperative endeavour to understand both how we could manipulate the immune system to our advantage, such as by improving the immune response against infections, increasing vaccine efficacy, boosting the anti-tumoral response, or knowing how to introduce a break in certain hyperinflammatory responses (e.g. severe COVID-19) (11), or autoimmune diseases (e.g. rheumatoid arthritis), characterized by chronic inflammatory responses against self-antigens, due to the loss of self-tolerance (12).

Two key cell types of the innate immune system are macrophages and dendritic cells (DCs) (13). Macrophages are tissue resident immune cells responsible for the maintenance of homeostasis of tissues under steady state. In response to inflammatory signals (Fig. 1) they can adopt pro-inflammatory functions characterized by the synthesis of pro-inflammatory cytokines (e.g. TNF and IL-6) (14,15). A few examples of classical inflammatory signals in macrophages are:

- Stimulation of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) by PAMPs and DAMPs, which activate different inflammatory pathways, depending on the TLR being stimulated (16–18);
- Binding of the Fc portion of antibodies to Fc receptors (FcR) present in the macrophages (19,20);

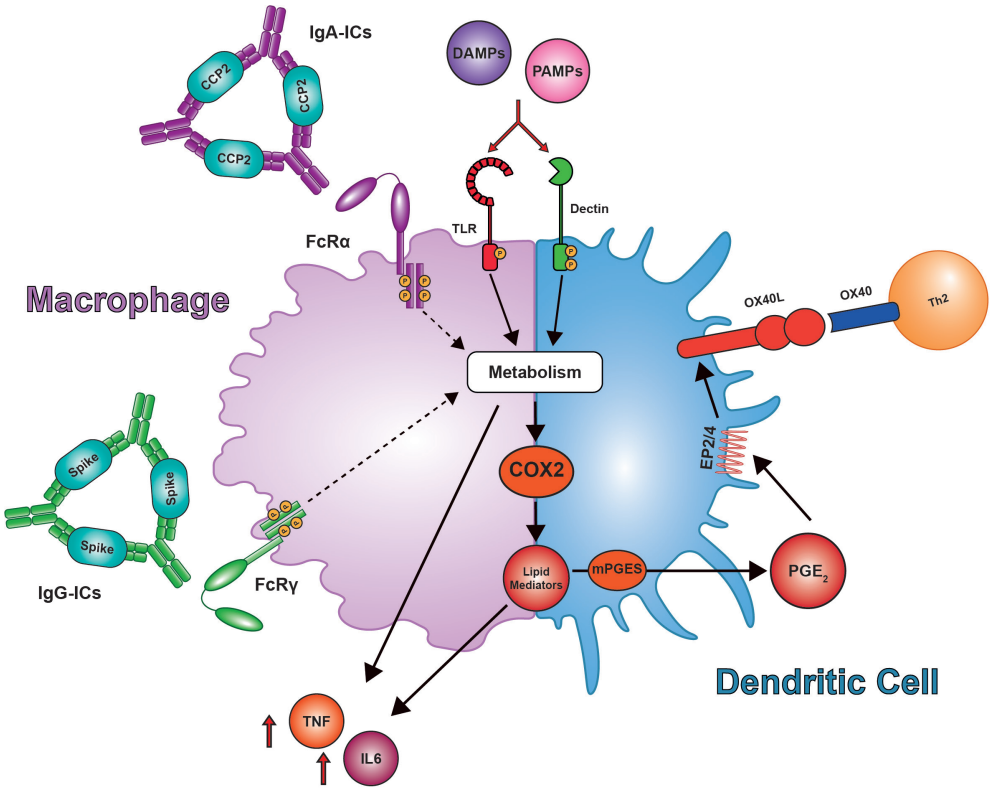

Figure 1: Metabolism and lipid mediators play a central role in innate immune cell function. Extrinsic stimuli induce metabolic changes in both macrophages and dendritic cells via PRRs (such as TLRs and Dectin), and/or via FcRs. These metabolic changes regulate the cellular immune response, via synthesis of COX2-dependent lipid mediators, and proinflammatory cytokines.

Predictably, these two stimuli can synergise and amplify the inflammatory phenotype of macrophages, thus mounting a stronger and more robust response against a pathogen, in cases where the Fc portion of the antibody engages an activating FcR (21–23). Alternatively, antibodies can also engage with inhibitory FcRs, thus dampening the overall inflammatory state of macrophages, and promoting tissue homeostasis (24).

While today it is known that macrophage differentiation and activation is a highly plastic process that exists on a spectrum, the two extremes of that spectrum are highly pro-inflammatory macrophages, commonly referred to as “M1-like”, and anti-inflammatory macrophages/macrophages that promote the resolution of the inflammatory process (i.e. pro-resolving macrophages), commonly referred to as “M2-like” (25). In general, macrophages with the M1-like phenotype are tasked with patrolling and killing

possible pathogens, through a process called phagocytosis and by the production of pro-inflammatory cytokines, while the M2-like promote wound healing, by producing anti-inflammatory cytokines, tissue regeneration and by engulfing dead cells, or cells undergoing cell death (i.e. apoptosis), through a process called efferocytosis (25).

On the other hand, the main function of DCs (Fig. 1) is to induce and direct the differentiation and activation of the adaptive immune system, especially through the presentation of antigens to T cells. Once DCs encounter an antigen, be it from an outside invader, such as a pathogen, or from an internal source (e.g. self-antigen or cancerous cell), they will undergo specific changes in activation, and either become immunogenic or tolerogenic. Immunogenic DCs will induce the differentiation and activation of cytotoxic CD8+ T cells, and/or CD4+ T helper cells, such as Th1, Th2 or Th17 cells, all with specific functions tailored to specific pathogens and immune challenges (26). Whereas tolerogenic DCs will instead induce the differentiation and activation of Treg cells, which work as built in immunologic brakes, that inhibit immune responses against a certain antigen, be it a self-antigen, to prevent autoimmunity, or against a foreign, but harmless, antigen such as foods (27,28).

In an impressive display of cellular coordination, the newly activated T cells, particularly Th1, Th2 or Th17, will migrate to the specific site where the presented antigen is located, and will oversee the immune response, by producing cytokines which will not only act on the innate immune system, such as the macrophages already present in the site, but also work as beacons to promote further migration of more innate immune cells to help fight against the specific threat (29–32).

Additionally, DCs can also activate Tfh cells (T follicular helper cells), which are intimately involved in initiating humoral immunity and shaping B cell responses (33,34). After this “activation trinity”, between B cells, DCs, and Tfh, B cells will migrate to the specific site the antigen presented by the DCs originated from, where they will then produce and secrete antibodies. These antibodies, usually in the form of IgG or IgA, are able to recognize the antigen and directly bind to it, forming immune complexes, which are then able to be recognized by macrophages, via Fc receptors (Fig. 1), thus helping these macrophages undergo further pro-inflammatory activation (35,36). These mechanisms put DCs as the first target in a strategy of immune manipulation, since they dictate the activation states of T cells and B cells, while it puts macrophages as the last target, since they are the final actors in this innate-adaptative-innate immunological chain.

Control of Macrophage and DC Function by Lipid Metabolism

One of the more recent fields of study in immunology is immunometabolism. This area arose from the discovery that, depending on the function being performed, immune cells will undergo specific metabolic reprogramming, favouring certain metabolic pathways over others, not only for their energetic needs, but also for the synthesis of crucial metabolites to be used in their activation and differentiation stages. For instance, it was described that, *generally*, pro-inflammatory macrophages and immunogenic DCs rely on glycolysis and fatty acid synthesis, while pro-resolving macrophages and tolerogenic DCs instead rely on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) (37–39). With this knowledge also came the hypothesis that, by manipulating macrophage and DC metabolism, one could control their activation state. For example, by inhibiting metabolic pathways favoured by pro-inflammatory/immunogenic phenotypes, and promoting metabolic pathways favoured by pro-resolving/tolerogenic phenotypes, the cell would switch from a pro-inflammatory state to an anti-inflammatory state, and vice-versa.

One crucial pathway at the centre of immunometabolism is lipid metabolism. While lipids have long been seen as molecules for energy storage and building blocks for membranes, we now know that is not the case. Lipid metabolism plays a central role in the synthesis of metabolites used by immune cells for their respective functions. For example, fatty acid synthesis can lead to the formation of lipid droplets in macrophages and DCs, which have been shown to play a role in immune functions, such as cytokine production, phagocytosis and antigen presentation (40–42). Alternatively, FAO was shown to be important Acetyl-CoA from fatty acid oxidation can be used for histone acetylation and subsequent control of gene transcription (43,44).

Additionally, lipid metabolism also includes the synthesis of lipid mediators. Lipid mediators are a group of metabolites that play a highly important role in cell messaging. As the name suggests, these metabolites originate from the oxidation of fatty acids, usually derived from membrane phospholipids, and act as chemical transductors of messages (Fig. 1). These mediators can act on the cell itself (autocrine signalling), on cells close by to the original cell (paracrine) or on cells far away from the cell of origin (endocrine). These mediators are one of the main communicators between immune cells, being able to induce signalling pathways in macrophages and DCs that either promote the synthesis of proinflammatory cytokines and T cell priming, or instead dampen inflammation, by promoting tissue regeneration and tolerogenicity (45). Thus, unravelling the mechanisms which lead immune cells to synthesize these lipid mediators and how these mediators act on the immune cells themselves

is crucial to shed a light on possible therapeutic targets for intervention from an immunometabolism point of view.

Nevertheless, much still remains unknown. As mentioned above, *in general*, pro-inflammatory macrophages and immunogenic DCs tend to favour glycolysis and fatty acid synthesis, while anti-inflammatory macrophages and tolerogenic DCs tend to prefer oxidative phosphorylation and fatty acid oxidation. However, subsequent studies have suggested that this immunometabolic dichotomy is not always so, showcasing that the metabolic reprogramming that macrophages and DCs undergo upon activation is dependent on a panoply of factors, such as cell type, tissue location, activation stimulus, and even timing. Therefore, it is crucial to look at the cellular immunometabolic profile in each specific context. Indeed, recent literature has shown that FAO is important for NLRP3 inflammasome activation and anti-tumor functions (46,47), while fatty acid synthesis appears to impair anti-tumour responses and is important for M2-like activation in helminth infections (48,49).

This seemingly contradictory information also holds true for the role of lipid mediators. For example, while in some contexts one lipid mediator (e.g. Prostaglandin E_2) can induce a pro-inflammatory response in macrophages, or drive a Th1-priming response by DCs, in other contexts it can instead induce an anti-inflammatory response and/or drive a Th2 response (50–62).

Therefore, considering there is a crucial need to look into the metabolic requirements of macrophages and DCs in specific contexts, this thesis aimed to address a few unanswered questions, such as:

1. What does the current literature show regarding the role of lipid metabolism in regulating the functions of DCs and macrophages in pro- and anti-inflammatory contexts?
2. What are the metabolic requirements of macrophages during antibody-mediated inflammation and what roles do lipid mediators play in driving this inflammatory response? Is there a difference between antibody isotypes and classes, or do all antibodies use the same metabolic pathways?
3. What is the role of lipid mediators during antigen recognition by DCs in the context of Th2-priming driven by eggs during helminth infections? Can this be chemically targeted to shift the balance towards a Th1-priming phenotype in DCs?

Thesis Outline:

Chapter 2 constitutes a more in-depth theoretical introduction to this thesis. There you can find a background into the field of immunometabolism in the context of innate immunity, with specific focus on fatty acid metabolism in DCs and macrophages, and how both metabolic profile and immune function are intricately connected.

In **chapter 3** we studied the role of SARS-CoV-2 anti-spike IgG in promoting an hyperinflammatory state in macrophages. IgG achieves this by inducing specific metabolic changes that prime these macrophages for excessive pro-inflammatory cytokine expression. By inhibiting these metabolic pathways we should they could be chemically targeted to prevent IgG-induced hyperinflammation. On a similar note, in **chapter 4** we looked at the role of IgA against citrullinated peptides in driving chronic inflammation in the context of rheumatoid arthritis. IgA achieves this by inducing a state of hyperinflammation in macrophages that is both dependent on certain metabolic changes and the synthesis of lipid mediators downstream of cyclooxygenase-2, thus identifying chemical targets with possible therapeutic applications in treating auto-antibody-driven chronic inflammatory diseases.

In **chapter 5** we describe how DCs recognize soluble egg antigens from the parasitic helminth *Schistosoma mansoni* through Dectin-2, how they become licensed to induce the differentiation of Th2 cells, and how can DC lipid mediator synthesis be chemically targeted to mould their immune function within this context.

In **chapter 6** I provide an extensive discussion outlining the novel findings of this thesis, and delve into future research suggestions to further decode the nuances of immunometabolism in the context of inflammatory responses, and the possible practical applications that this scientific information may have on society as a whole.

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